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The Role of Platelets in Allergic Inflammation and Asthma

Mirjana Turkalj and Ivana Banic

Abstract

Platelets are a kind of blood cells derived from bone marrow megakaryocytes and play essential roles in thrombosis, hemostasis, and tissue repair. Platelets have been found to be crucially involved in various immune responses and actively involved in the pathogenesis of allergic diseases such as allergic asthma. Patients with allergic asthma have lower platelet counts and increased levels of markers of platelet activation after allergen exposure. Platelets have been found extravascularly in the airways, and platelet products have been measured in bronchoalveolar lavage (BAL) fluid of asthmatic patients. Platelets are also crucially involved in the development of allergic diseases, including the development of allergic asthma via the regulation of allergic inflammation, especially type 2 inflammation mediated by active platelet-derived IL-33 protein activation. Both platelets and IL-33 are activated by tissue damage and involved in biological defense mechanisms and initiation of tissue repair. Therefore, platelets may be involved in the development of steroid-refractory asthma, including irreversible airway remodeling phenotypes.

Keywords: platelets, immune response, asthma, allergic inflammation, IL-33

1. Introduction

Platelets, also known as thrombocytes (from the Greek words *thrombos* meaning clot and *kytos* meaning a vessel, i.e., a cell), are blood components with a well-established role in hemostasis and thrombosis. Platelets are circulating anuclear cell fragments ca. 2 μm in diameter derived from megakaryocytes of the bone marrow, and their production (as well as megakaryocyte production) is regulated by thrombopoietin (also known as megakaryocyte growth and development factor, MGDF). About 10^{11} new platelets are produced daily in a healthy adult individual, and the average life span of circulating platelets is up to 10 days. Platelets respond to vascular injury by clumping and initiation of blood clotting [1]. More specifically, when blood vessels are damaged and bleeding occurs, immediate and appropriate actions are required to prevent excessive blood loss and to repair tissue damage, including injured blood vessels, and platelets play a central role in these processes. The immediate response to vascular injury and bleeding is vasoconstriction, and soon after that, platelets, which normally circulate the bloodstream in a quiescent state due to certain inhibitory signals, adhere and accumulate at the site of vascular endothelium damage. They become activated and release the contents of their granules containing adenosine diphosphate (ADP), thromboxane A2 (TXA2), calcium, platelet-activating factor (PAF), serotonin, etc. This further promotes platelet aggregation and the formation of a temporary and unstable platelet plug
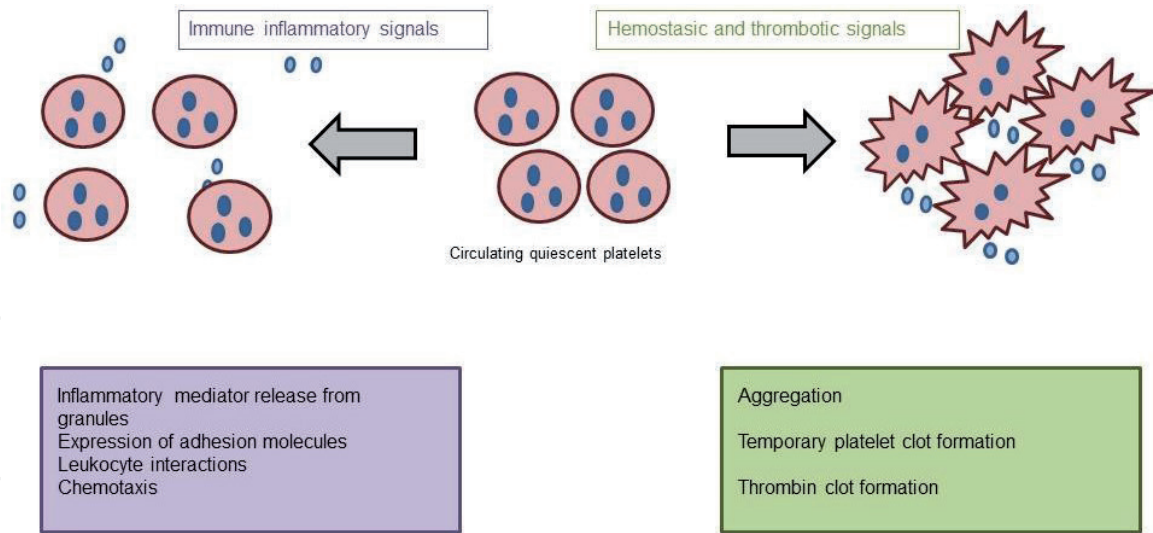
Figure 1.
Dichotomy of platelet functions and activation. Depending on the type of activation signals and mechanisms (prothrombotic or inflammatory), platelets may exhibit either hemostatic and thrombotic (on the right, green box) or proinflammatory effects (on the left, purple box). Red objects indicate platelets (quiescent or activated), while blue objects represent platelet granules.

in a process referred to as primary hemostasis. The activation of a number of coagulation factors leads to the formation of a fibrin mesh which then covers the platelet plug, generating a stable fibrin clot (a process called secondary hemostasis). Logically, once their hemostatic function ceases, clots must be degraded and removed and the tissue damage at the clot site repaired [2, 3]. Undamaged vascular endothelial cells surrounding the clot produce tissue plasminogen activator (tPA) which catalyzes the conversion of plasminogen to active plasmin, a key enzyme involved in clot degradation (fibrinolysis), while the platelets are removed by phagocytosis. Additionally, platelets contain a number of cell and transforming growth factors, including transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF), which play important roles in tissue repair [4].

Since platelets seem to be involved in all processes in response to hemorrhage, including primary and secondary hemostasis, fibrinolysis, and tissue repair, it is conceivable that they may be critical in maintaining the physical barriers to external attacks such as pathogen invasion, including the epithelial barrier integrity and function as well as immune responses, and the body of evidence to support that theory is growing. Indeed, it seems that platelets function quite differently in inflammatory immune responses than they do in hemostasis and thrombosis. Moreover, there are specific and distinct physiological signals and mechanisms in platelet functions involving aggregation (in hemostasis) and those involving immune processes, such as communication and interactions with leukocytes, platelet chemotaxis, as well as direct antimicrobial effects [5]. This has led to the hypothesis of a dichotomy in platelet activation—coagulation vs. their involvement in a plethora of physiologic immune reactions, as well as inflammatory disorders including allergic diseases and asthma [6]. A summary of the dual nature of platelet functions and activation mechanisms is represented in **Figure 1**.

2. Platelet function in the innate and acquired immune responses

Other than posing a risk for serious bleeding, vascular injury represents a significant risk of pathogen invasion. Hence, in addition to a thrombin clot preventing

further blood loss, a functional immunological barrier must be formed at the site of vascular damage as soon as possible in order to prevent the spreading of bacteria, viruses, and other pathogens into the body. Platelets exhibit important functions in assisting and directly modulating inflammatory immune responses, which is why they can be considered vital contributors to the integrity of the immunological barrier. These include mechanisms of both the innate and adaptive immunity.

2.1 Immunothrombosis

Tightly regulated and directed thrombosis (called immunothrombosis) in response to vascular injury serves to locally prevent the spread of pathogens to the bloodstream. This process is orchestrated in concordance with platelets and other immune cells, such as neutrophils and monocytes, and initiated either by classical immune cells via their pattern recognition receptors (PRRs) or by the binding of platelets to bacteria. Platelets bind to pathogenic bacteria either directly via thrombocytic pattern recognition receptors to epitopes on bacterial surface or by other plasma proteins that bridge platelets and bacteria [7, 8].

In the process of immunothrombosis, monocytes respond to bacterial pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by activating extrinsic coagulation pathways with tissue factors (tissue thromboplastin).

Additionally, along with their classical phagocytosis function in response to pathogen invasion, neutrophils facilitate this process by eliminating pathogens by throwing web-like implements or neutrophil extracellular traps (NETs). This process is known as NETosis and represents an alternative type of cell death (other than apoptosis or necrosis). Neutrophils activated in this manner release nuclear DNA and antimicrobial proteins including elastase and myeloperoxidase extracellularly by disrupting their own cell membrane. Pathogens captured by these net-like structures are more easily being phagocytosed. In turn, platelets seem to facilitate NETosis. Platelets are activated, among other stimuli, by binding lipopolysaccharide (LPS) on Gram-negative bacteria via the Toll-like receptor-4 (TLR4). Such activated platelets express P-selectin (or CD62P), a cell adhesion molecule vital in leukocyte recruitment (including neutrophils) to sites of injury via their ligand P-selectin glycoprotein ligand-1 (PSGL-1). This signaling pathway further activates neutrophils to release larger amounts of NETs, and it seems that platelet-neutrophil interactions are essential in the production of NETs since platelet depletion or the disruption of platelet-neutrophil interactions resulted in the proliferation and further diffusion of bacteria in a murine sepsis model. Moreover, NETs also bind tissue factor and activate the intrinsic coagulation pathway by providing its negatively charged surface to the coagulation factor XII and thus participate in immunothrombosis [2, 9–17].

2.2 Platelets are immune cells, de facto

Although they are usually viewed as anuclear cell fragments originating from megakaryocytes involved in hemostasis and thrombosis, platelets exhibit virtually all characteristics of classical immune cells. They contain a number of immune-associated molecules in their intracellular granules, such as P-selectin stored in α-granules in circulating quiescent platelets [18]. When platelets are activated (e.g., by thrombin or ADP), P-selectin is immediately translocated to the plasma membrane [19]. There, it acts as a receptor or ligand for its counterpart expressed on the surface of other immune cells (PSGL-1), such as neutrophils (as described above), monocytes, and lymphocytes, and it is vital for the initiation of the recruitment of

these cells to the site of interest [10, 11]. Once activated, platelets secrete a number of other immune-associated molecules, such as chemokines, cytokines, lipid mediators, and growth factors that modulate the inflammatory immune response at the site of vascular injury [4].

Additionally, platelets possess the ability to kill pathogens in both an indirect manner (by recruiting other immune cells) and even directly. Indeed, platelets store a number of molecules with strong antimicrobial potency in their α-granules called platelet microbicidal proteins (PMPs) [20, 21], such as the chemokines CXCL4 (or platelet-factor 4, PF-4) and CXCL-7 (or neutrophil-activating peptide-2, NAP-2) [22, 23]. When activated and bound to bacteria opsonized by immunoglobulin G (IgG), platelets release reactive oxygen species (ROS), antimicrobial peptides, defensins, kinocidins, and proteases, thus killing the pathogen directly [24]. Moreover, other than their involvement in NETosis-mediated pathogen destruction, platelets are involved in other processes directed against microbes involving eosinophil functions similar to NETosis. More specifically, eosinophils and even mast cells are known to produce extracellular DNA traps similar to NETs (called eosinophil extracellular traps, EETs in eosinophils), and certain platelet-derived factors (PAF in combination with IL-5 and GM-CSF) may be involved in the induction and propagation of EETosis [25]. Platelets also express Toll-like receptors 1 through 4 (TLR1-4) and TLR6-9, thus facilitating antigen recognition (PAMPs) and innate immune responses in pathogen destruction [26, 27].

Platelets also express functional receptors of both high and low affinity for immunoglobulins (FcγRI, FcγRII, FcγRIII, FcεRI, FcεRII, FcαRI, etc.) suggesting an important role in adaptive immune response. Moreover, activated platelets express both CD40 and its ligand (CD40L, CD154), which are crucial in antigen presentation to effector cells (T lymphocytes) [28]. Platelet-derived CD40L is also involved in the maturation and activation of dendritic cells (DCs) even extravascularly [29] as well as in the production of T-dependent isotype switching [30].

All of these, along with platelet ability to undergo phagocytosis [31] and chemotaxis to the tissue of interest, emphasize the vital role of platelets in both innate and adaptive immune responses and define them as immune cells de facto. As such, platelets are involved in the pathogenesis of a number of immune disorders, including allergic inflammation and asthma.

3. Role of platelets in allergic inflammation and bronchial asthma

As mentioned before, since platelets may very well be considered immune cells and due to their role in the functioning and integrity of the epithelial and immunological barrier, they are involved in the pathogenesis of a number of chronic diseases, including cancer and inflammatory disorders. Platelet abnormalities in allergy have long been reported, and numerous studies since have underpinned their importance in the regulation of allergic inflammation.

As mentioned before, platelets express both the high- and low-affinity IgE receptors on their surface, and moreover, in allergic donors, exposure to the sensitizing allergen leads to the production of a number of inflammatory mediators, such as serotonin and CCL5 or "regulated on activation, normal T cell expressed and secreted" (RANTES) [32, 33]. In mice with ovalbumin (OVA)-induced allergic inflammation, platelets from ovalbumin-sensitized animals, but not those lacking the high-affinity IgE receptor, migrated extravascularly to the lungs in response to allergic stimuli, thus suggesting that platelets actively participate in antigen-dependent allergic inflammation, including early phases, and via IgE-mediated mechanisms [34].

Additionally, platelets seem to be important for the recruitment of antigen-specific activated T lymphocytes (CD69+ CD4+ T cells) into inflamed airways in patients with allergic asthma. Platelets adhere to the vascular endothelial cells in the airways, and the protein myosin light-chain 9/12 (Myl9/12) in platelets is released to form net-like structures intravascularly. Myl9/12 binds to its ligand on CD69+ T cells and aids their extravasation and migration to the inflamed lungs. In an asthma murine model, blocking of the Myl9/12-CD69 interaction results in reduced airway eosinophilia, indicating that platelets may be crucial for antigen-specific T-cell responses [35].

Exposure to the sensitizing allergen leads to platelet activation in patients with allergic asthma. This allergen challenge may result in a mild peripheral thrombocytopenia (reduced number of platelets), probably due to localized airway recruitment of platelets and the presence of platelet-leukocyte complexes in the blood. Patients with asthma have increased levels of platelet-derived mediators, such as PAF-4, β-thromboglobulin (β-TG), RANTES, and thromboxane, both in the peripheral blood and bronchoalveolar lavage (BAL) fluid, suggesting increased levels of platelet activation. Such platelets are referred to as "exhausted" platelets due to their continuous activation in allergic inflammation, which is why allergic patients may exhibit a mild hemostatic effect associated with shortened platelet survival time and slightly prolonged bleeding time [28]. The role of platelet activation in allergic inflammation reflects also in the fact that an elevated number of platelet precursors (megakaryocytes) has been found in patients who have died of status asthmaticus (an extreme form of asthma exacerbation) [36].

As mentioned before, platelets also produce mitogens, such as TXA2, PDGF, EGF, and vascular endothelial growth factor, which promote airway cell proliferation [37]. Additionally, platelets themselves produce extracellular matrix modifying enzymes and thus participate in airway remodeling characteristic in allergic disorders, such as smooth muscle cell hyperplasia and collagen deposition [5]. Platelet depletion in a murine allergic model resulted in decreased epithelial thickening, smooth muscle thickening, and subepithelial fibrosis [38].

During allergic sensitization, platelets may be activated by the upregulation of their expression of CD154 (CD40L), which plays a central role in mediating the interactions between APCs and lymphocytes. More specifically, platelet-derived CD154 is involved in a number of immune responses, including endothelial cell response, T-helper cell priming, and activation of cytotoxic T lymphocytes. In a murine OVA-induced allergic asthma model, platelet transfer seemed to promote allergic inflammation by enhancing leukocyte infiltration to the affected organ, enhancing the production of IgE, and propagating T-helper type 2 (Th2)-mediated immune responses. On the other hand, platelet depletion in such mice failed to promote asthma development, suggesting that CD154 (CD40L) derived from platelets is required in the progression of allergic asthma. Moreover, platelets seem to inhibit the induction of FoxP3+ regulatory T cells via CD154-mediated mechanisms, which further supports the theory of the vital role of platelet CD154 in allergic disease progression by polarizing Th2-mediated and modifying (inhibiting) Treg-mediated immune responses [39].

In summary, allergic inflammatory stimuli (exposure to a sensitizing allergen) leads to specific platelet activation (other than that in hemostasis, supporting the theory of the dichotomy in platelet functions): the production of a number of inflammatory mediators, such as ROS, RANTES, and 5-hydroxytryptamine (5-HT), a potent spasmogen and bronchoconstrictor, and the generation of platelet-leukocyte complexes resulting in the activation and migration of inflammatory cells to the tissue of interest, thus promoting allergic inflammation and platelet chemotaxis to the affected tissue further propagating the inflammatory immune response. This is schematically represented in **Figure 2**.
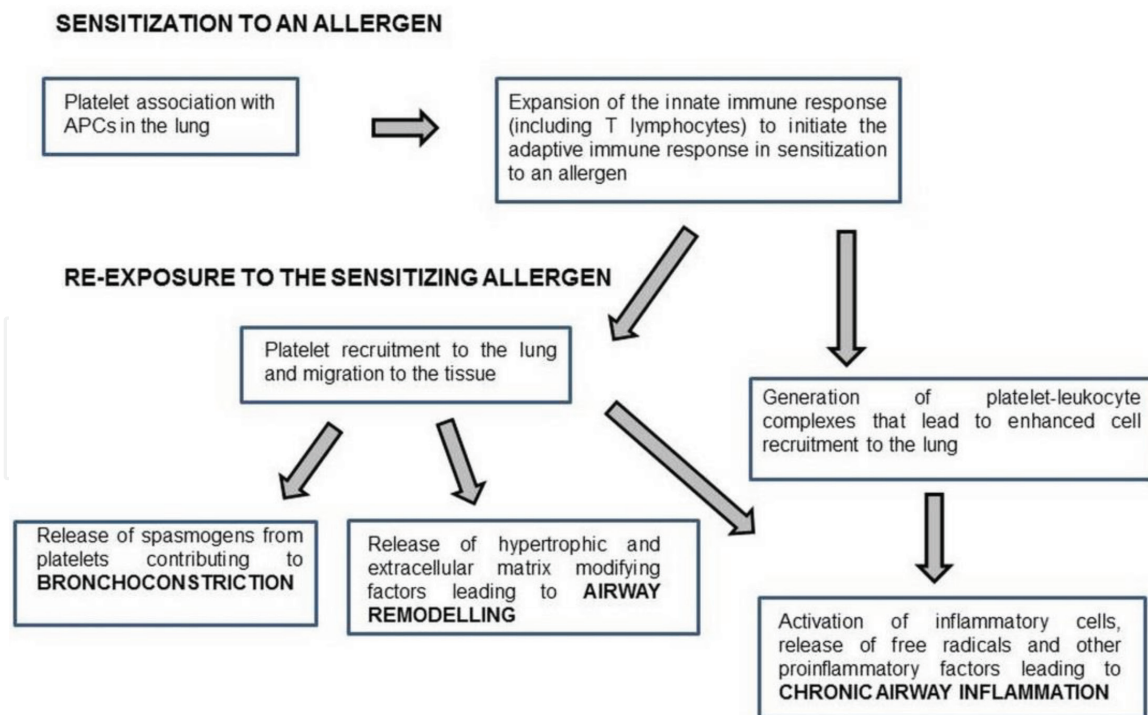
Figure 2.
A summary of the role of platelets in allergic inflammation, more specifically in asthma pathogenesis, in both the sensitization (allergen priming) and subsequent re-exposure phases. APCs, antigen-presenting cells.

4. Role of IL-33 in the immune response

Interleukin-33 (IL-33) is essential in the regulation of innate immune responses, and the body of evidence to underpin its vital role in allergic inflammation and pathogenesis of allergic disorders is growing. IL-33 is a member of the IL-1 super-family of cytokines that is expressed on a number of cells, including mast cells, DCs, macrophages, fibroblasts, as well as endothelial and epithelial cells. It is a ligand for the interleukin 1 receptor-like 1 (IL1RL1) which is highly expressed on Th2 cells, mast cells, and group 2 innate lymphocytes (ILC2s) [40]. IL-33 exhibits a dual nature in function—it acts as a nuclear factor (binding to DNA) intracellularly and as cytokine extracellularly. As a cytokine, it acts as a potent driver of the production of Th2-cytokines, such as interleukin-4 (IL-4) from Th2 cells, mast cells, eosinophils, and basophils [41, 42].

Genome-wide association studies (GWAS) have identified the *IL33* gene and its receptor (IL1RL1/ST2) as susceptibility loci in allergy and asthma [43, 44].

IL-33 acts as an "alarmin", a factor rapidly released from damaged tissue that serves to alert the immune system of a potential threat of infection. IL-33 is released by necrotic cells after tissue injury and subsequently acts on target cells. In response to IL-33, ILC2s exhibit a strong antigen-non-specific Th2 inflammatory response, suggesting their role in allergy and asthma pathogenesis [2]. ILC2s are activated by IL-33 alone or in combination with IL-2 and subsequently produce large amounts of type 2 cytokines, such as interleukin-5 (IL-5) and interleukin-13 (Il-13) [45]. Intranasal administration of IL-33 to mice significantly induced airway hyperresponsiveness and type 2 inflammation [46]. Moreover, human airway epithelial cells and microvascular endothelial cells in the lung express IL1RL1 and respond to IL-33 stimuli which leads to a rapid production of neutrophil-attracting chemokines [40]. In hemostasis, platelet-derived IL-33 acts on intact tissue cells in proximity of injured blood vessels to produce large amounts of CXCR2 chemokines, thus recruiting neutrophils to the site of injury. Activated platelets further act on

neutrophils to release NETs and stimulate neutrophil migration and phagocytosis [2, 40]. Moreover, platelets constitutively express the full length IL-33 and are crucial in the development of papain-induced airway eosinophilia in a murine model via an IL-33-dependent mechanism [47].

IL-33 is also thought to accelerate Th17 cell-mediated airway inflammation via mast cells [48].

5. Platelet-eosinophil interactions in asthma

In asthmatic patients, eosinophilic inflammation is associated with type 2 inflammation; therefore, the interactions between eosinophils and platelets during allergen exposure may be important for the pathogenesis of allergic asthma. In patients with allergic asthma, links in activity between eosinophils and platelets have been found. Levels of ECP and P-selectin as markers of activation of eosinophils and platelets, respectively, were found and suggested a positive association between eosinophils and platelets, which was negatively associated with asthma-related quality of life [49]. Ex *vivo* measurements of eosinophils isolated from patients with asthma have shown that they adhere to endothelial cells more compared to eosinophils from healthy subjects, and platelets seem to promote this adhesion [50]. It is known that the mechanism of interaction between platelets and eosinophils is associated with increased expression of adhesion molecules on activated cells. Expression of P-selectins on platelets was essential for the recruitment of eosinophils into the lung, following allergen challenge [49]. Soluble P-selectins enhanced activation of α4β1-integrin on eosinophils and stimulate eosinophil adhesion to vascular cell adhesion molecule-1, *in vitro* [51]. After antigen challenge of asthmatic patients, circulating eosinophils associated with P-selectin decreased because of migration of platelet-eosinophil complexes into the lungs [52]. In addition to this mechanism, the interaction between platelets and eosinophils occurs indirectly *via* inflammatory mediator release, such as chemokine PF-4 which is capable of promoting eosinophil-endothelial adhesion due to upregulation of adhesion molecules [53]. The relationship between platelets and eosinophils is synergistic. Eosinophils release cytokines such as platelet-activating factor (PAF) and major basic protein (MBP) which can stimulate and activate platelets [54]. A recent study reported that platelet aggregation was inhibited by the eosinophil cationic protein (ECP) and eosinophil supernatant [55]. The role of eosinophils in platelet aggregation and thrombosis is not yet clear [56]. Certainly there is a therapeutic potential in disrupting eosinophil-platelet interactions in asthmatic patients inhibiting platelet activation and release of platelet cytokines or platelet interaction with other inflammatory cells such as eosinophils. Further research of the interaction between platelets and eosinophils may lead to the design of new therapeutic regimes in allergic asthma [5, 47].

6. Conclusions

Due to the multiplicity of their role in the immune response, platelets can be considered immune cells *de facto*, and there is mounting evidence on their importance in allergic inflammation and asthma pathogenesis. They contribute to all phases of the allergic inflammatory response, including sensitization and subsequent functional and structural changes of the affected tissue, thus perpetuating the chronicity of allergic inflammation. Both platelets and IL-33, an alarmin molecule, are vital in the maintenance and integrity of the immunological barrier.

Moreover, platelets constitutively express IL-33, providing continuous activation signals to target cells, including mast cells and ILCs2, which is crucial in allergic inflammation. Consequently, an emerging therapeutic potential in the inhibition of platelet-dependent inflammation in asthmatic patients may exist.

Conflict of interest

The authors have no conflicts of interest to declare.

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